

What is claimed is:

1. A method of treating a microbial infection in a subject, other than by hyperbaric oxygen therapy, the method comprising:
 - 5 (a) providing an oxygenating agent;
 - (b) administering an effective dosage of said oxygenating agent to said subject.
- 10 2. The method of treating a microbial infection as claimed in claim 1, wherein said oxygenating agent is at least one member selected from the group consisting of (i) a blood substitute based on cell-free hemoglobin and heme products and (ii) encapsulated hemoglobin and heme products.
- 15 3. The method of treating a microbial infection as claimed in claim 2, wherein said oxygenating agent is at least one member selected from the group consisting of (a) synthetic heme compounds, wherein said synthetic heme compounds are modified heme compounds having an alkaneimidazole group binding iron at the proximal sixth coordination site and with four long-chain alkanephosphocholine groups which provide lipophilicity and an oxygen pocket; (b) liposome-encapsulated hemoglobin
20 preparations, which can function as artificial red blood cells; and (c) modified hemoglobins.

4. The method of treating a microbial infection as claimed in claim 3, wherein said oxygenating agent is selected from the group consisting of Pyridoxalated Hemoglobin Polyoxyethylene Conjugate ("PHP"); PEG-hemoglobin; o-Raffinose Poly Hemoglobin ("Hemolink"); Polynitroxyl-Hemoglobin ("PNH"); polymerized human hemoglobin ("Poly SFH-P"); polymerized purified bovine hemoglobin; and cross-linked hemoglobins.
5. The method of treating a microbial infection as claimed in claim 4, wherein said cross-linked hemoglobin is Diaspirin Crosslinked Hemoglobin ("DCLHb", HEMASSIST™).
6. The method of treating a microbial infection as claimed in claim 1, wherein said oxygenating agent is a non-hemoglobin, non-heme material that dissolves oxygen, said material comprising synthetic chemical compounds of the class of agents known as perfluorocarbons (PFCs).
7. The method of treating a microbial infection as claimed in claim 6, wherein said synthetic chemical compounds are selected from the group consisting of perfluorodecalin ($C_{10}F_{18}$), perfluoro-tri-n-propylamine ($C_9F_{21}N$), fluoromethylo- adamantane ("FMA"), OXYGENT® (perfluorooctylbromide), PERFLUBRON® ($C_8F_{17}Br$), FLUOSOL-DA®, or any other perfluorocarbon derivative now or in the future known in the art.

8. The method of treating a microbial infection as claimed in claim 1, wherein said oxygenating agent is a non-hemoglobin, non-heme material that dissolves oxygen, said material being water supersaturated with oxygen to form Aqueous Oxygen®, said Aqueous Oxygen® then being perfused to produce regional or
5 systemic hyperoxemia.
9. The method of treating a microbial infection as claimed in claim 1, wherein said oxygenating agent generates oxygen by a chemical reaction.
- 10 10. The method of treating a microbial infection as claimed in claim 9, wherein said oxygenating agent is selected from the group consisting of hydrogen peroxide, tetrachlorodecaoxide, ozone, and potassium permanganate.
11. The method of treating a microbial infection as claimed in claim 1, wherein
15 said subject is a human.
12. The method of treating a microbial infection as claimed in claim 1, wherein the oxygenating agent is delivered topically for intradermal, subcutaneous or intramucosal penetration.
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13. The method of treating a microbial infection as claimed in claim 12, wherein said oxygenating agent is formulated in non-encapsulated pharmaceutical compositions to produce a formulation capable of penetrating the layers of the dermis

or the mucosa.

14. The method of treating a microbial infection as claimed in claim 13, wherein
said formulation is selected from the group consisting of penetrating emollients and
5 carriers on transdermal patches.

15. The method of treating a microbial infection as claimed in claim 14, wherein
said formulation is dimethylsulfoxide ("DMSO").

10 16. The method of treating a microbial infection as claimed in claim 12, wherein
said oxygenating agent is formulated in an encapsulated pharmaceutical composition
or a microencapsulated pharmaceutical composition, said formulation penetrating the
layers of the dermis or the mucosa.

15 17. The method of treating a microbial infection as claimed in claim 16, wherein
said formulation is encapsulated in a carrier comprising a form composed of at least
one member selected from the group consisting of lipids, amino acids, and/or other
types of polymers.

20 18. The method of treating a microbial infection as claimed in claim 17, wherein
said form is selected from the group consisting of spheres (liposomes), microspheres,
cochlear shapes, and dendrimers

19. The method of treating a microbial infection as claimed in claim 18, wherein said microspheres comprise at least one member selected from the group consisting of natural polymers, proteins, carbohydrates and waxes.

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20. The method of treating a microbial infection as claimed in claim 19, wherein said microspheres comprise at least one member selected from the group consisting of gelatin, albumin, casein, gum arabic, gum acacia, agar, alginates, carrageenan, starches, xanthan, beeswax and shellac.

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21. The method of treating a microbial infection as claimed in claim 19, wherein said microspheres comprise at least one member selected from the group consisting of cellulose esters, cellulose ethers, fatty acid derivatives and fatty alcohol derivatives.

15 22. The method of treating a microbial infection as claimed in claim 19, wherein said microspheres comprise at least one member selected from the group consisting of methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate butyrate, sodium carboxymethyl cellulose, cellulose nitrate, glyceryl-mono-, di-, or tri-stearate, stearic acid, aluminum monostearate, glyceryl mono- and di-palmitate, hydrogenated tallow,
20 12-hydroxy-stearyl alcohol, hydrogenated castor oil, cetyl alcohol, and myristyl alcohol (1-tetra-decanol).

23. The method of treating a microbial infection as claimed in claim 19, wherein said microspheres comprise synthetic polymers.

5 24. The method of treating a microbial infection as claimed in claim 23, wherein said synthetic polymer is selected from the group consisting of (a) vinyl polymers and copolymers, (b) polyamides and polyesters, (c) polymers prepared by interfacial polymerization, (d) waxes and resins and (e) amino resins, alkyd resins, epoxy-resins, polyester resins, polydimethyl siloxane, and polycarbonates.

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25. The method of treating a microbial infection as claimed in claim 24, wherein said synthetic polymer is selected from the group consisting of polyvinyl alcohol, polyacrylamide and copolymers, ethylene-vinyl acetate copolymers, polymethyl methacrylate, polyvinyl pyrrolidone, polystyrene, styrene-acrylonitrile copolymers, 15 polyvinylidene chloride, vinyl ether copolymers, carboxyvinyl polymers ("Carbopol"), nylon 6-10, polylysine and copolymers, polyglutamic acid and copolymers, polylactic acid and copolymers, hydrogel polymers (polyhydroxyethyl methacrylate and copolymers), polyglycolic acid, polyurethanes, paraffin wax and hydrocarbon wax.

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26. The method of treating a microbial infection as claimed in claim 19, wherein

said microspheres comprise polymers that degrade in a predictable manner, wherein said time-released delivery of said oxygenating agents is controlled.

27. The method of treating a microbial infection as claimed in claim 26, wherein
5 the microspheres comprise poly-lactide-co-glycolide, said microspheres being administered to the subject as a subcutaneous implant.

28. The method of treating a microbial infection as claimed in claim 1, wherein
said oxygenating agent is delivered by a needle-injection method selected from the
10 group consisting of subcutaneously; directly into a superficial infection (such as a boil) or into a deep infection (such as an intra-abdominal abscess); intramuscularly; intravenously; intra-arterially; intracardiac; intrapericardiac; intrathecal; by lumbar puncture; or by burr hole directly onto the meninges or into the parenchyma of the brain.

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29. The method of treating a microbial infection as claimed in claim 1, wherein
said oxygenating agent is delivered by a delivery method selected from the groups
consisting of (a) by intravascular catheter for perfusion of the large vessels of an
organ, for example in order to perfuse an infarcted and infected bowel segment; (b)
20 instillation tube, for example for instillation into the abdominal cavity in the case of an abscess; (c) by catheter to irrigate the lumen of a hollow organ (such as the urinary bladder and the uterus), or the lumen of the gastrointestinal tract (some segments of which provide an anaerobic or microaerophilic milieu that favors the multiplication of

pathogens, as for example in Helicobacter pylori infections of the stomach or duodenum and the ulcers concomitant therewith, and Crohn's disease and/or ulcerative colitis, these being conditions well known to be controlled with the prescription of various antibiotics); and (d) by endoscopic instrument, for example for
5 irrigation of (i) the fallopian tubes or of (ii) the apical segments of the lung (these segments being relatively poorly oxygenated and therefore prone to low-level colonization by Mycobacterium tuberculosis).

30. The method of treating a microbial infection as claimed in claim 1, wherein
10 said oxygenating agents are incorporated into bandages, dressings and/or packings, (i) for superficial or deep wounds, (ii) for incisions, (iii) for fistulae, and/or (iv) for the prophylactic protection of areas of the skin that are prone to develop or are already developing pressure sores, gangrene, or cellulitis.

15 31. The method of treating a microbial infection as claimed in claim 1, wherein said oxygenating agents are incorporated into toothpastes, gels and/or packings that can be used by the patient or inserted by the dentist, in the treatment and prevention of periodontal disease and the bone loss concomitant therewith.

20 32. The method of treating a microbial infection as claimed in claim 1, wherein said infecting microbe is any type of bacterium, virus, yeast, fungus, mold, algae or parasite (protozoa, amoeba, or other form).

33. The method of treating a microbial infection as claimed in claim 1, wherein said infecting microbe can be from any group, but is particularly one generally recognized as being difficult to treat, therefore rendering the infected human or
5 animal in need of an adjunctive treatment such as that of the present invention.

34. The method of treating a microbial infection as claimed in claim 1, wherein said microbe is difficult to treat by virtue of its location being a hypoxic/ischemic site, which condition results in a decreased rate of microbial replication, thereby rendering
10 said locus of microbes unresponsive to those antimicrobial agents that require active replication for effectiveness.

35. The method of treating a microbial infection as claimed in claim 34, wherein said microbe is selected from the group consisting of S. aureus, P. aeruginosa, S. typhimurium, E. coli, S. pyogenes, Serratia marcescens, P. mirabilis, C. albicans, and
15 M. tuberculosis.

36. The method of treating a microbial infection as claimed in claim 1, wherein said microbe is difficult to treat by virtue of its being in a location into which it is
20 difficult for antimicrobial agents to diffuse.

37. The method of treating a microbial infection as claimed in claim 36, wherein said location is selected from the group consisting of intracellular locations such as macrophages, T cells, neurons and hepatocytes; any walled-off area, such as an abscess or a tubercle; inside a body cavity; inside a sac (such as the pericardium); inside a joint; in the recesses of bone; in the lumen of a hollow organ (e.g., the gastrointestinal tract, urinary bladder, genital organs, and upper and lower respiratory tract and the sinuses thereof); in a periodontal site; or in the linings of any organ (e.g., peritoneum, pleural lining, and the meninges or other linings of the brain).

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38. The method of treating a microbial infection as claimed in claim 1, wherein said microbe is difficult to treat by virtue of its being a strain that is multidrug resistant.

15 39. The method of treating a microbial infection as claimed in claim 38, wherein said microbe is selected from the group consisting of vancomycin-resistant *Enterococcus faecium* and vancomycin intermediate-resistant or vancomycin-resistant *Staphylococcus aureus*.

20 40. The method of treating a microbial infection as claimed in claim 1, wherein said microbe is one that can be directly harmed by increases in pO₂.

41. The method of treating a microbial infection as claimed in claim 40, wherein said microbe is selected from the group consisting of Clostridium difficile, Clostridium perfringens, Propionibacterium acnes and Porphyromonas gingivalis.

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43. The method of treating a microbial infection as claimed in claim 1, wherein said microbe is one that can be indirectly harmed by increases in pO_2 , in that said increase will augment the innate host antimicrobial defenses (such as the oxidative burst of professional phagocytes, which burst is oxygen-dependent).

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44. The method of treating a microbial infection as claimed in claim 43, wherein said augmentation is an increased ability under a higher pO_2 of various white blood cells to generate free radicals that will in turn kill intracellular specimens of (i) S. typhimurium and of (ii) the Human Immunodeficiency Virus.

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45. The method of treating a microbial infection as claimed in claim 1, further comprising adjunctive synergistic agents, singly or in various combinations or permutations, being co-administered with the oxygenating agent, either together in a pharmaceutical co-formulation, or separately in time and space.

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46. The method of treating a microbial infection as claimed in claim 45, wherein

said adjunctive synergistic agent is an antimicrobial agent appropriate to the infecting microbe.

47. The method of treating a microbial infection as claimed in claim 46, wherein said
5 antimicrobial agent is an antibacterial agent.

48. The method of treating a microbial infection as claimed in claim 47, wherein
said antibacterial agent is one selected from the group consisting of antibiotics;
chemotherapeutic agents (such as sulfamethoxazol); bacteriophages and defective
10 bacteriophages; bacteriocins and bacteriocin-like substances ("BLSs"); defensins and
all related peptide-based antibacterial agents; therapeutic antibodies or vaccines
administered acutely to treat an infection; and sterilizing agents and disinfecting
agents.

15 49. The method of treating a microbial infection as claimed in claim 48, wherein
said bacteriophages, which cannot efficiently propagate (if at all) when the bacterial
target is in a hypoxic milieu (and is therefore not dividing), said bacteriophages will
be made more efficient by the present invention, whether they be wild-types, or
strains patented on account of special characteristics (such as long circulation time
20 and therefore delayed clearance by the RES).

50. The method of treating a microbial infection as claimed in claim 47, wherein said antimicrobial agent is specific for viruses, said antimicrobial agent being selected from the group consisting of AZT, Zovirax, and interferons.

5 51. The method of treating a microbial infection as claimed in claim 47, wherein said antimicrobial agent is specific for yeasts, said agent being selected from the group consisting of Nystatin and Vagistat.

52. The method of treating a microbial infection as claimed in claim 47, wherein
10 said antimicrobial agent is specific for fungi, said agent being selected from the group consisting of Amphotericin B, abelcet, and ketoconazole.

53. The method of treating a microbial infection as claimed in claim 47, wherein said antimicrobial agent is specific for parasites, whether unicellular or multicellular,
15 said agent being selected from the group consisting of Flagyl, iodoquin, quinine, atabrine, and comparable anti-parasitic medications known in the art.

54. The method of treating a microbial infection as claimed in claim 45, wherein said adjunctive synergistic agent is an antioxidant, said antioxidant being selected
20 from the group consisting of tocopherol (vitamin E), catalase, ascorbic acid and superoxide dismutase ("SOD").

55. The method of treating a microbial infection as claimed in claim 45, wherein said adjunctive synergistic agent is an endotoxin antagonist, said antagonist being selected from the group consisting of monoclonal antibodies, or derivatives of
5 reconstituted high density lipoproteins ("rHDL").

56. The method of treating a microbial infection as claimed in claim 45, wherein said adjunctive synergistic agent is a cytokine modulator that attenuates the deleterious effects of the infecting microbes and their toxins. Examples would include
10 monoclonal antibodies directed against pro-inflammatory cytokines (e.g. IL-6, TNF), soluble receptors for those cytokines, and/or drugs that block the translocation of transcription factors (such as but not limited to NF-kappaB) that would otherwise increase the synthesis and release of said pro-inflammatory cytokines.

57. The method of treating a microbial infection as claimed in claim 45, wherein
15 said adjunctive synergistic agent is a growth factor that can help the repair and healing of a tissue, said agent being selected from the group consisting of epithelial growth factors (EGFs) and would also include interferons, anti-inflammatory cytokines, chemokines, and MHC type 2 -inducing or -modulating factors.

58. The method of treating a microbial infection as claimed in claim 45, wherein said
20 adjunctive synergistic agent is an agent that induced angiogenesis and thereby speeds the healing of wounds, examples including but not being limited to becaplermin.